Evidence would currently suggest that meso-level or macro-level approaches are needed; however, whether these interventions could be done in a manner that results in equitable reductions in LRI morbidity and mortality is unclear.

The GBD 2017 Lower Respiratory Infections Collaborators' Article[3] is an important step in quantifying broader priority areas for the prevention of paediatric pneumonia and in highlighting areas in which successes have been achieved. However, the development of local capacity to collect, analyse, and report on LRI-specific indicators needs to be intensified to ensure high-quality data for stakeholders to act effectively. We hope this work will further galvanise and build on global commitments to accelerate progress towards LRI morbidity and mortality targets and encourage funding to establish sustainable data structures and rigorously evaluate equitable effects of interventions both between and within regions.

*Carina King, Eric D McCollum
Department of Public Health Sciences, Karolinska Institutet, Stockholm, Sweden (CK); Institute for Global Health, University College London, London WC1N 1EH, UK (CK); Eudowood Division of Pediatric Respiratory Sciences, Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, MD, USA (EDMcC); and Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (EDMcC)
c.king@ucl.ac.uk

We declare no competing interests.

1 Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016; **388:** 3027–35.
2 Brown R, Head M. Sizing up pneumonia research: assessing global investments in pneumonia research 2000–2015. Southampton: University of Southampton, 2018.
3 GBD 2017 Lower Respiratory Infections Collaborators. Quantifying risks and interventions that have affected the burden of lower respiratory infections among children younger than 5 years: an analysis for the Global Burden of Disease Study 2017. *Lancet Infect Dis* 2019; published online Oct 30. https://doi.org/10.1016/S1473-3099(19)30410-4.
4 Li Y, Reeves RM, Wang X, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. *Lancet Glob Health* 2019; **7:** e1031–45.
5 Menon P, Nguyen PH, Mani S, Kohli N, Avula R, Tran LM. Trends in nutrition outcomes, determinants, and interventions in India (2006–2016). New Delhi: Poshan, 2017.
6 Masoud S, Menon P, Bhutta ZA. Addressing child malnutrition in India. In: Preedy VR, Patel VB, eds. Handbook of famine, starvation, and nutrient deprivation: from biology to policy. Cham: Springer, 2019: 93–108.
7 Dahlui M, Azahar N, Oche OM, Aziz NA. Risk factors for low birth weight in Nigeria: evidence from the 2013 Nigeria Demographic and Health Survey. *Glob Health Action* 2016; **9:** 28822.
8 National Population Commission. Nigeria demographic and health survey 2018—key indicators report. Abuja, and Rockville, MD: National Population Commission and ICF, 2019.
9 Mortimer K, Balmes JR. Cookstove trials and tribulations: what is needed to decrease the burden of household air pollution? *Ann Am Thorac Soc* 2018; **15:** 539–41.

Turning influenza vaccinology on its head to reveal the stalk

Published **Online** October 17, 2019 https://doi.org/10.1016/S1473-3099(19)30556-0

See **Articles** page 80

Inactivated influenza virus vaccines (IIVs) have been in use for more than 70 years with no major changes in the underlying technology. Limitations of these vaccines include the long production cycle, which requires strain selection well in advance of their use; provision of only moderate protection when vaccine strains match circulating strains; protection that wanes quickly; potential issues with repeated annual immunisation, such as reduced haemagglutination-inhibition boosting and protection from infection; and no protection against novel outbreak or pandemic strains.[1] IIVs primarily work by stimulating antibodies against the head domain of the haemagglutinin protein, but these antibodies are undermined by rapid antigenic drift in circulating strains. Therefore, improvements in influenza vaccine design are urgently needed.

The haemagglutinin stalk has higher sequence conservation and a slower rate of adaptation than the head domain[2] owing to its key role in membrane fusion during viral entry. A haemagglutinin stalk-specific monoclonal antibody, C179, was first described in mouse H2N2 vaccination studies in 1993,[3] and the haemagglutinin stalk was revitalised as a vaccine target following the 2009 H1N1 pandemic.[4] Since then, broadly reactive haemagglutinin-stalk monoclonal antibodies have been further developed as therapeutics and vaccine strategies.[5] One promising vaccination strategy involves chimerisation of the haemagglutinin protein to encode the haemagglutinin head domain from a strain that has not infected humans, such as avian H8, and the conserved haemagglutinin H1 stalk domain to boost existing antibodies against the subdominant haemagglutinin stalk, with striking results in preclinical trials in mice,[6] pigs,[7] and ferrets.[8]

In *The Lancet Infectious Diseases*, David I Bernstein and colleagues[9] report interim results of a randomised,

observer-blinded, multicentre, phase 1 study of chimeric group 1 haemagglutinin vaccines using live-attenuated influenza viruses (LAIVs) or IIV with or without the oil-in-water AS03 adjuvant. The five-group study in 65 adults included two placebo control groups and three vaccine regimens: prime vaccination with LAIV expressing an H8/1 chimera followed by booster vaccination with IIV expressing an H5/1 chimera, with or without AS03 adjuvant, and prime vaccination with AS03-adjuvanted IIV expressing an H8/1 construct followed by booster vaccination with AS03-adjuvanted IIV expressing an H5/1 construct.

All vaccine regimens were well tolerated, with no unexpected adverse events in the aggregate results. The interim results of peripheral, systemic immune responses to prime and boost vaccines were assessed by ELISA-based quantification of haemagglutinin stalk and cross-reactive antibodies and memory B cells and plasmablasts. The IIV prime with AS03 adjuvant resulted in substantial boosting of anti-H1 stalk antibodies and cross-reactive antibodies to the group 1 haemagglutinin proteins H2, H8, and bat-derived H18, accompanied by expansion of plasmablasts and memory B cells. By contrast, the LAIV prime had minimal effect on systemic antibodies and B cells. After heterologous boost with the IIV vaccine 2 months later, there was a minimal increase in anti-haemagglutinin stalk antibody titres in the group that also received IIV as the prime vaccine. Individuals primed with LAIV and boosted with IIV plus AS03 reached a similar titre of H1 stalk-specific antibodies as in the group primed and boosted with IIV vaccine but had no increase in peripheral H1 stalk-specific memory B-cell responses, suggesting a cap on haemagglutinin stalk antibody concentrations or vaccine immunogenicity. The inclusion of an adjuvant, AS03, clearly enhanced haemagglutinin stalk antibody titres, consistent with previous studies.[10] Data were not presented on the effect of LAIV on local antibodies, antibody effector function, and T-cell responses, but work is ongoing to elucidate these effects.

Most importantly, this study shows that haemagglutinin stalk antibodies can be boosted by chimeric haemagglutinin vaccines in adults. Therefore, steric hindrance for B-cell receptor access to the haemagglutinin stalk domain appears not to be a limiting factor to immunogenicity, but overcoming the immunodominance of existing B-cell memory responses to the haemagglutinin head domain does. Therefore, vaccinating individuals with pre-exisiting haemagglutinin-stalk responses will require novel vaccine design and approaches to overcome haemagglutinin-head immundominance, turning influenza vaccine strategies on their head.

The universal influenza vaccine field is an expanding area. In early 2019, a haemagglutinin stalk-based vaccine entered phase 1 trials that uses a ferritin-nanoparticle haemagglutinin ministalk protein (NCT03553940). Another haemagglutinin stalk approach using supra-seasonal universal IIV (NCT03275389) was suspended by GSK after an interim phase 1 analysis found poor immune responses upon heterologous boost (NCT03814720). An LAIV with a defective M2 protein, M2SR by FluGen, is also being assessed in phase 1 trials in children. Phase 2 and 3 trials are ongoing for universal vaccine candidates that stimulate T-cell responses, including conserved peptides (NCT03058692) and a live vaccinia backbone, MVA plus NP/M1 (NCT03883113). Lessons will be learnt from each trial—the development of a broadly protective universal influenza vaccine will be an iterative process to optimise design and strategy—but these trials show encouraging progress on the path towards universal influenza vaccines.

Sophie A Valkenburg, Benjamin J Cowling
HKU-Pasteur Research Pole, School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China (SAV); and World Health Organization Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, The University of Hong Kong, Hong Kong Special Administrative Region, China (SAV, BJC)
sophiev@hku.hk

BJC has received honoraria from Sanofi Pasteur and Roche. SAV declares no competing interests.

1 Valkenburg SA, Leung NHL, Bull MB, et al. The hurdles from bench to bedside in the realization and implementation of a universal influenza vaccine. *Front Immunol* 2018; **9:** 1479.
2 Kirkpatrick E, Qiu X, Wilson PC, Bahl J, Krammer F. The influenza virus hemagglutinin head evolves faster than the stalk domain. *Sci Rep* 2018; **8:** 10432.
3 Okuno Y, Isegawa Y, Sasao F, Ueda S. A common neutralizing epitope conserved between the hemagglutinins of influenza A virus H1 and H2 strains. *J Virol* 1993; **67:** 2552–8.
4 Wrammert J, Koutsonanos D, Li GM, et al. Broadly cross-reactive antibodies dominate the human B cell response against 2009 pandemic H1N1 influenza virus infection. *J Exp Med* 2011; **208:** 181–93.
5 Sautto GA, Kirchenbaum GA, Ross TM. Towards a universal influenza vaccine: different approaches for one goal. *Virol J* 2018; **15:** 17.

6 Nachbagauer R, Kinzler D, Choi A, et al. A chimeric haemagglutinin-based influenza split virion vaccine adjuvanted with AS03 induces protective stalk-reactive antibodies in mice. *NPJ Vaccines* 2016; **1:** 16015.
7 Sunwoo SY, Schotsaert M, Morozov I, et al. A universal influenza virus vaccine candidate tested in a pig vaccination-infection model in the presence of maternal antibodies. *Vaccines (Basel)* 2018; **6:** e64.
8 Nachbagauer R, Miller MS, Hai R, et al. Hemagglutinin stalk immunity reduces influenza virus replication and transmission in ferrets. *J Virol* 2015; **90:** 3268–73.
9 Bernstein DI, Guptill J, Naficy A, et al. Immunogenicity of chimeric hemagglutinin-based universal influenza virus vaccine candidates: interim results of a randomised, placebo-controlled, phase 1 clinical trial. *Lancet Infect Dis* 2019; published online Oct 17. https://doi.org/10.1016/S1473-3099(19)30393-7.
10 Khurana S, Coyle EM, Manischewitz J, et al. AS03-adjuvanted H5N1 vaccine promotes antibody diversity and affinity maturation, NAI titers, cross-clade H5N1 neutralization, but not H1N1 cross-subtype neutralization. *NPJ Vaccines* 2018; **3:** 40.

Alternative hepatitis B vaccine strategies in healthy non-responders to a first standard vaccination scheme

Hepatitis B virus (HBV) infection is a major public health problem with an estimated 257 million people with chronic HBV infection and around 650 000 annual deaths due to long-term HBV-related liver disease (cirrhosis and hepatocellular carcinoma).[1] Vaccination represents the cornerstone of public health measures to eradicate HBV. The implementation of effective infant vaccination programmes in many countries has resulted in a significant decrease in the prevalence of HBV infection and in the incidence of liver cancer in children and young adults.[1–3]

Besides universal childhood vaccination, most countries also recommend HBV vaccination to high-risk adults with three-dose series HBV vaccine at 0, 1, and 6 months. Because of factors such as age, male sex, obesity, smoking, chronic alcohol consumption, and DRB1 and DQB1 HLA class II alleles, 5–30% of immunocompetent individuals do not develop HBV seroprotection defined as an antibody titre against hepatitis B surface antigen (anti-HBs) of 10 IU/L or more (measured one to three months after the last vaccination), defining them as non-responders.[4,5] In such a situation, it is recommended to give 1–3 additional doses of vaccine with anti-HBs dosage after each injection until seroprotection is achieved. This schedule usually results in 38% of responses after one and 80% after three additional doses.[6,7] In immunocompromised patients, the percentage of non-responders is higher and more immunogenic strategies are recommended. The use of high dose HBV vaccine in patients with HIV as well as the use of adjuvanted vaccine in patients on haemodialysis have shown good results for increasing the seroconversion rate.[8,9] Such alternative strategies—usually higher doses of HBV vaccine and vaccine combining HBsAg with other antigen and adjuvanted vaccine—have also been considered in healthy non-responders. They have been proved equivalent in a meta-analysis of 16 studies with a high disparity in design, methodology, and number of vaccine doses received before enrolment.[7]

In this issue of *The Lancet Infectious Diseases*, Stijn Raven and colleagues[10] report the results of a randomised, open-label, parallel group, controlled, multicentre superiority trial done in the Netherlands comparing the immunogenicity and safety of four different vaccination schemes in healthy non-responders. Between 2012, and 2017, 480 participants (mean age 45 years) were randomly assigned to one of the following four groups: repeating initial series for the control group (HBVaxPro 10 µg or Engerix-B 20 µg), combined vaccine against hepatitis A and hepatitis B (Twinrix 20 µg), AS04-adjuvanted vaccine (Fendrix 20 µg), or higher antigen dose vaccine (HBVaxPro 40 µg). All revaccination schedules consisted of a single intramuscular dose administered in the deltoid region at months 0, 1, and 2. The median interval between the completion of the primary series and the start of the revaccination series was roughly 3 months. More than 95% completed the full revaccination series.

After a median interval of 37 days after the third revaccination, seroprotection was observed in 67% in the control group, 80% in the Twinrix group, 83% in the HBVaxPro-40 group, and 87% in the Fendrix group. After adjustment for centre effect, differences in proportions of responders were significant for HBVaxPro-40 and Fendrix compared with the control group (22% and 26%). Likewise, geometric mean titre ratios were significantly higher for the HBVaxPro-40 and Fendrix groups compared with the control group (3·7 and 5·4).

After stratification according to baseline anti-HBs concentrations (zero responders group=anti-HBs<1 UI/L *vs* poor responders=anti-HBs [1–9·9] UI/L),

iStock/Manjunul

Published **Online**
October 16, 2019
https://doi.org/10.1016/S1473-3099(19)30582-1

See **Articles** page 92